Original Article

A Case-Control Study of the Relationship between Gastric Cancer and Meat Consumption in Iran

Neda Zamani MSc[1], Majid Hajifaraji PhD•[2], Akbar Fazel-tabar Malekshah PhD[3], Abbas Ali Keshtkar PhD[4], Ahmad Esmaillzadeh PhD[5], Reza Malekzadeh MD[3]

Abstract

Background: Despite the descending trends of gastric cancer in many parts of the world, its mortality rate has still remained high globally. Meat, red and processed meat in particular, may induce gastric carcinogenesis through potential mechanisms. However, the role of this dietary aspect in the risk of gastric cancer has not well been investigated so far. Therefore, we designed a study to assess the relation between meat consumption and the risk of gastric cancer in Golestan Province, a high- risk area for gastric malignancies in Iran.

Methods: Subjects of this population-based case-control study included 190 histologically confirmed cases of gastric cancer and 647 controls. Meat consumption was evaluated using a 116-item semi-quantitative food frequency questionnaire. A lifestyle questionnaire also collected data concerning demographic features, anthropometric measures, and other known risk factors of gastric cancer. We estimated crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the relation between meat intake and gastric cancer.

Results: After being adjusted for potential confounders, red meat intake was positively associated with gastric cancer which reached statistical significance (OR = 1.87, 95% CI: 1.01–3.47, P_{trend} = 0.07). On the other hand, individuals in the highest quartile of white meat consumption had a statistically significant reduced risk of gastric cancer compared to those in the lowest quartile (OR = 0.36, 95% CI: 0.19–0.68, P_{trend} = 0.005).

Conclusions: We observed a positive association between red meat consumption and the risk of gastric cancer, and a reverse relationship regarding white meat intake and the risk of this malignancy.

Keywords: Gastric cancer, Iran, red meat, white meat

Introduction

The incidence and mortality rates of gastric cancer have faced a remarkable decline in many parts of the world during the last half century.[1] Based on recent estimates; however, gastric malignancies are still the second major cause of cancer mortalities worldwide and therefore account for a crucial health concern.[2]

In Iran, gastric malignancies are the most common fatal cancers and their incidence rates are above the world's average.[3] Ardabil Province located in the north west of Iran ranks the first in gastric malignancies in the country with the age standard incidence rates of 49.1 and 25.4 for males and females, respectively.[4] It's worth mentioning that Golestan Province in the north east of Iran is reported among the high-incidence rate areas of gastric cancer in the country, as well.[5]

Diet has been postulated as an important aspect in the etiology of gastric cancers[6] and many studies have been carried out on the associations between various dietary constituents and these malignancies.[7]

Meat is a food component which its consumption has increased considerably worldwide.[8] The major cancer type that has so far been persuasively linked to high amounts of meat consumption is colorectal cancer. Nonetheless, the positive association for other gastrointestinal malignancies such as gastric cancers is not still conclusive and requires additional investigation. In other words, cumulative results from prior studies conclude that the evidence regarding both red and processed meat intake and the risk of gastric cancers has not yet been sufficient and compatible enough to reach out a consensus.[9]

A number of potential mechanisms are proposed through which meat might provoke the formation of particular carcinogenic compounds such as heterocyclic amines (HCAs), N-nitroso compounds (NOCs), and polycyclic aromatic hydrocarbons (PAHs).[10] These compounds are likely to be produced either during cooking or due to endogenous reactions. It is also suggested that both hem iron content and high energy density of meat might also contribute to carcinogenesis. All these mechanisms can yield to a connection between meat intake and cancer risk.[10]

In Iran, only a limited number of studies have investigated the role of some dietary factors including fruits, vegetables, dairy products,[11] tea consumption,[12] and vitamin deficiencies[13] in the causation of upper gastrointestinal cancers. However, there has been an apparent lack of investigation regarding the association of meat intake and the risk of gastric cancer. Hence, to expand upon previous findings, we designed a study in Golestan Province,

Authors' affiliations: [1]Faculty of Nutrition Sciences and Food Technology, International Branch of Shahid Beheshti University of Medical Sciences, Tehran, Iran. [2]National Nutrition and Food Technology Research Institute, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [3]Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. [4]Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran. [5]Department of Nutrition, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran.

•**Corresponding author and reprints:** Majid Hajifaraji PhD, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, 3# Baran, West Arghavan, Farahzadi Blvd., Shahrak Qods, P. O. Box: 1981619573, Tehran, Iran. Tel: +98-212-236-0661-2, Fax: +98-212-237-6467, E-mail: m.hajifaraji@nnftri.ac.ir.

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which as mentioned before is a high-risk area for gastric malignancies. The aim of this study was to explore the relation between meat consumption and the risk of gastric cancer in the study area.

Materials and Methods

Definition and selection of subjects

Subjects within this study were requited from the previous Golestan case-control study. In brief, this study was performed to assess the relation between opium use and the risk of gastric cancers.[14] Cases of the mentioned study were recruited from 2004 through 2011 at the Atrak Clinic, which is a specialized referral clinic for upper digestive tract malignancies instituted by the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences in eastern Golestan. All local physicians are proclaimed to refer their patients suspicious of having upper gastrointestinal (GI) cancers to this clinic. Cases were confirmed histopathologically and qualified for taking part if being 18 years old or higher, living in the catchment area at the time of enrolment, and having no prior or simultaneous history of any cancers.[15] Controls were identified from the Golestan Cohort study. Briefly, the Golestan Cohort study is a prospective study in Golestan province with initial aim of exploring the etiology of upper gastrointestinal malignancies in the region. The study recruited 50045 healthy inhabitants (40–75 years old) between 2004 and 2008. Details of the cohort study have already been published.[16] For our study, we randomly selected 675 controls from the cohort, with no matching, for 198 gastric cancer cases that were recruited at Atrak Clinic. Of these subjects included in the study, we omitted three cases and 10 controls who had implausible energy intake estimates (mean ± 3SD) and five cases and 18 controls who failed to complete the food frequency questionnaire (FFQ) sufficiently. These exclusions yielded a total number of 190 cases and 647 unmatched controls to be considered for statistical analysis.

Data collection and dietary assessment

At baseline, for cases after being diagnosed at the Atrak Clinic and for controls after being registered in the cohort study, a trained physician interviewed each subject to fill out a structured lifestyle questionnaire. In brief, this questionnaire collected information regarding demographic features; anthropometric measures; socioeconomic status (SES)[15]; residential, occupational, smoking , and medication histories; and other known potential confounders. Besides, a trained nutritionist fulfilled a 116-item FFQ for each subject. This semi-quantitative FFQ was designed exclusively for this region based on food choices and preferences of the inhabitants. The validity and reliability of the FFQ were previously assessed using twelve 24-hr recall questionnaires, four FFQs, and biochemical measurements at the pilot phase of the Golestan Cohort Study.[17] The FFQ evaluated the consumption frequency and portion sizes of foods and beverages during the prior twelve months. Portion sizes and daily nutrient intakes (grams/day) were calculated using the US Department of Agriculture Food Consumption Table, release 23. We classified meats into two groups of red and white meats. Lamb, beef, liver and other viscera, hamburgers, hot dogs, sausage, and cold cuts were regarded as red meats. White meats also included chicken, poultry, and fish. Meats contained within mixed dishes, such as pizza and stew, were categorized according to their respective meat type.

To evaluate *H. pylori* infection, blood samples were sent to the German Cancer Research Center located in Heidelberg, Germany, where *H. pylori* multiplex serology method was administered to distinguish CagA-positive *H. pylori*-infected subjects.[18]

The protocol of this study was approved by the ethical review boards of the DDRC, NCI, and IARC. Besides, written informed consents were also obtained from each participant at the time of initial enrolment.

Statistical analysis

Firstly, energy-adjusted means of red and white meat consumption were calculated using Residual Method. Then subjects were categorized into quartiles based on red and white meat intake. Means of quantitative variables among the quartiles of red and white meat consumption were compared using one-way ANOVA test. Chi-square test and Chi-square for trend test were also administered to compare qualitative variables among the quartiles of meat consumption. Means of food groups intake adjusted for age, sex, and energy were computed among the quartiles of red and white meat consumption using the General Linear Model and the means were then compared by ANCOVA test. To assess the relation between red and white meat consumption and the risk of gastric cancer, the Logistic Regression Model was used. The risk of gastric cancer was first estimated among the quartiles of red and white meat intake in the row model. Next, in the multivariate model the aforesaid relation was evaluated after being adjusted for the variables of age (30–50, 51–70, >71 years old), sex (qualitative), energy intake (kcal/day), ethnicity (qualitative), hot tea consumption (qualitative), tooth brushing (yes/no), cigarette smoking (yes/no), SES (high, average, low), literacy (literate/illiterate), opium consumption (yes/no), grains intake (quartiles), dairy consumption (quartiles), and vegetable (quartiles) and fruit (quartiles) intake. The interaction between red and white meat intake was also taken under control in the adjusted model. To assess P_{trend} for ORs among the quartiles of red and white meat intake, the medians of red and white meat consumption in each quartile were first calculated and then used as quantitative variables in the Logistic Regression Model.

Results

Table 1 presents the baseline characteristics of the case and control groups in the study. As stated, Cases of gastric cancer were more likely to be older, heavier, and therefore to have higher body mass index (BMI) compared to healthy individuals within the control group. Besides, they were less likely to be married and of Turkmen ethnicity. They were also more probable to be illiterate and considerably much more willing to drink hot tea than the control group. In addition, they consumed more opium and did not brush their teeth for at least once a day. However, surprisingly, they were less cigarette smokers compared to the control group.

Regarding energy, food groups, and nutrients intake, it was observed that daily calorie intake of cases was higher than that of controls (Table 2). The mean of total meat intake was significantly higher in cases (89.2 ± 89.9 g/d) versus controls (88.4 ± 69.2 g/d). The same pattern was also perceived regarding red meat consumption (22.5 ± 27.3 g/d compared to 17.1 ± 16.9 g/d). Inversely, the intake of white meat was higher in controls rather than cases (71.2 ± 66.0 g/d versus 66.7 ± 85.4 g/d). Considering other food groups, cases consumed more dairy, fruits, grains, and oil per day compared to the healthy individuals.

Table 1. Baseline characteristics of the case and control groups in the study.

Characteristics	Cases (*n* = 190)	Controls (*n* = 647)	*P*-value
Age (years)*	65.3 (11.2)	61.4 (10.3)	<0.001
Sex (% men)*	68.9	66.9	0.6
Weight (kg) *	66.3 (14.0)	58.1 (13.4)	<0.001
BMI (kg/m²)*	25.5 (5.1)	21.9 (4.9)	<0.001
SES (score)*	12.9 (5.3)	13.2 (5.5)	0.5
Area (% rural)	63.2	65.5	0.5
Ethnicity (%Turkmen)	51.6	66.9	<0.001
Marital status (% married)	76.3	88.1	<0.001
Literacy (% illiterate)	81.6	72.6	0.01
Cigarette smoking (% current smoker)	10.0	13.9	0.03
Opium use (% users)	33.2	19.6	<0.001
Alcohol consumption (% consumers)	4.2	7.1	0.2
Tooth brushing (% not brushers)	77.9	62.6	<0.001
Tea temperature (% hot tea drinkers)	62.6	30.9	<0.001
H. pylori infection (% +HPMS)	85.3	82.8	0.5
BMI = body mass index, SES = socio-economic status, * mean (SD)			

Table 2. Daily energy, food groups, and nutrients intake of the case and control groups in the study.

Energy intake*	Cases (*n* = 190)	Controls (*n* = 647)	*P*-value
Energy (kcal/day)	2508 (789)	2150 (606)	<0.001
Energy from carbohydrate (%)	54.4 (9.3)	56.2 (7.3)	0.006
Energy from fat (%)	35.1 (8.6)	31.9 (6.3)	<0.001
Energy from protein (%)	12.8 (3.4)	14.1 (3.2)	<0.001
Food groups *			
Total meat (g/d)	89.2 (89.9)	88.4 (69.2)	0.01
Red meat	22.5 (27.3)	17.1 (16.9)	<0.001
White meat	66.7 (85.4)	71.2 (66.0)	0.02
Dairy (g/d)	262.0 (173.4)	217.5 (145.3)	0.02
Fruits (g/d)	217.3 (202.6)	139.8 122.4)	<0.001
Vegetables (g/d)	120.5 (87.7)	134.1 (92.1)	0.07
Grains (g/d)	433.4 (156.0)	407.6 (156.7)	0.046
Fat and oil (g/d)	47.3 (33.3)	31.0 (20.3)	<0.001
*mean (SD)			

Individuals in the highest versus the lowest quartiles of red meat consumption were more likely to be of a higher SES and alcohol consumers. Besides, they tended to consume more fruits and vegetables and fewer grains (g/d). On the contrary, those in the lowest compared to the highest quartiles had a greater propensity to be rural, illiterate, and consumed more energy (kcal/d), mainly from carbohydrate and less from fat sources (Table 3).

With regard to white meat consumption, individuals in the lowest quartile tended to be older, of a higher SES, to have a slightly more BMI, and to consume more vegetables (g/d) compared to ones in the highest quartile of white meat intake. Moreover, the percentage of energy allocated from fat and protein sources were higher in the highest versus the lowest quartiles of white meat intake. On the other hand, those in the lowest quartile were more likely to be married, opium users, hot tea drinkers, and consumed more grains (g/d). They also had a greater propensity to consume more energy, mainly derived from carbohydrate sources (Table 3).

Total red meat consumption (fresh and processed red meat) showed a very slight, not statistically significant, decreased risk of gastric cancer in the row model (OR for the highest versus the lowest quartiles of red meat intake: 0.92, 95% CI: 0.61–1.39; P_{trend}: 0.001) (Table 4). After being adjusted for potential confounders, however, a positive association was observed between total red meat intake and the risk of gastric cancer in the multivariable-adjusted model (OR: 1.87, 95% CI: 1.01–3.47; P_{trend}: 0.07). Regarding white meat consumption (poultry and fish), a statistically significant inverse association was observed in the row model (OR for the highest versus the lowest quartiles of white meat intake: 0.48, 95% CI: 0.31–0.75; P_{trend}: <0.001). This protective role was still detected in the multivariable-adjusted model which also reached statistical significance (OR: 0.36, 95% CI: 0.19–0.68; P_{trend}: 0.005).

Discussion

This population-based case-control study was designed to explore the relationship between meat consumption and gastric cancer in Iran. The results revealed a statistically significant elevated risk of gastric cancer regarding total red meat intake (fresh red meat and processed red meat). On the other hand, individuals in the highest quartile of white meat consumption (poultry and fish) showed a reduced risk of gastric cancer compared to those in the lowest quartile which also reached statistical significance.

Several studies with case-control designs have been carried out so far to assess the relation between red and processed meat intake and the risk of gastric cancers.[9,19] Some have shown a statistically significant elevated risk concerning fresh red meat[20,21] or processed meat intake[21–24] and the risk of gastric cancer. While, some others either reached no statistical significance or found no associations for red[23,25–27] or processed meat intake.[25,28,29] The same pattern is also perceived within cohort studies. In some research an increased risk of gastric cancer was observed regarding fresh red meat[30] and processed meat intake.[30,31] Whereas, others have seen no associations either for red[32–34] or processed meat[33,35,36] in this regard. As a result of no consensus, a report released in 2007 concluded that the current evidence is not convincing enough to judge a positive association regarding red or processed meat intake and the risk of gastric cancers.[9]

Table 3. Baseline characteristics, energy, and food groups intake among the quartiles of red and white meat consumption.

Characteristics	Quartiles of red meat					Quartiles of white meat				
	Q_1	Q_2	Q_3	Q_4	P-value	Q_1	Q_2	Q_3	Q_4	P-value
Age (years) *	62.5(9.7)	62.2(10.5)	61.2(10.5)	59.8(10.4)	0.08	59.6(10.5)	59.9(10.6)	62.2(10.2)	63.9(9.3)	<0.001
Sex (% men)	28.2	22.5	20.7	28.5	0.04	32.4	23.6	20.7	23.2	0.02
Weight (kg) *	66.4(13.8)	64.9(14.0)	65.4(13.3)	68.4(14.8)	0.1	66.9(14.1)	64.3(12.9)	67.4(14.1)	66.5(14.7)	0.2
BMI (kg/m^2) *	25.5(4.8)	25.2(5.4)	25.2(4.7)	26.2(5.4)	0.2	25.6(5.0)	24.5(4.8)	26.1(5.0)	25.8(5.4)	0.03
SES (score) *	11.7(4.1)	13.1(5.6)	13.7(5.4)	14.3(6.3)	<0.001	12.1(5.1)	12.5(5.8)	14.1(5.4)	14.0(5.2)	0.001
Area (% rural)	31.4	24.6	21.3	22.6	<0.001	29.2	24.3	21.7	24.8	0.6
Ethnicity (% Turkmen)	24.9	23.9	24.7	26.6	0.2	30.5	25.4	22.2	21.8	0.06
Marital status (% married)	27.6	23.1	22.5	26.9	0.6	31.2	24.1	21.5	23.2	0.004
Literacy (%illiterate)	30.7	23.7	22.2	23.4	<0.001	30.9	22.7	23.0	23.4	0.4
Cigarette smoking (% current smoker)	22.9	22.9	21.1	33.0	0.5	34.9	22.9	21.1	21.1	0.8
Opium use (% users)	31.1	18.9	20.5	29.5	0.2	37.4	21.1	16.3	25.3	0.01
Alcohol consumption (% consumers)	13.0	25.9	18.5	42.6	0.01	22.2	22.2	24.1	31.5	0.5
Tea temperature (% hot tea drinkers)	31.3	22.6	21.3	24.8	0.2	34.5	23.5	21.3	20.7	0.04
H. pylori infection (% +HPMS)	27.5	23.4	22.8	26.4	0.9	29.7	22.5	23.6	24.2	0.6
Energy (kcal/d) *	2388(544)	2019(484)	1991(589)	2207(704)	<0.001	2304(683)	2086(584)	2037(509)	2174(606)	0.001
Energy from carbohydrate (%) *	58.0(8.4)	56.2(6.9)	56.3(6.6)	54.4(6.9)	<0.001	60.8(6.8)	57.9(6.1)	55.6(5.4)	50.6(6.8)	<0.001
Energy from fat (%) *	30.5(6.4)	31.8(5.8)	31.7(6.0)	33.4(6.6)	0.001	30.1(7.0)	31.8(6.3)	32.4(5.4)	33.2(6.0)	<0.001
Energy from protein (%) *	13.8 (3.5)	14.2(3.3)	14.2(3.1)	14.3(2.8)	0.3	11.6(1.7)	12.7(1.6)	14.2(1.5)	17.9(3.2)	<0.001
Dairy (g/d) *	226.6(162.1)	195.2(146.8)	203.4(123.5)	245.2(142.4)	0.06	213.4(143.3)	204.8(121.8)	233.4(170.2)	218.5(141.8)	0.05
Fruits (g/d) *	126.4(125.1)	128.3(97.2)	138.0(103.1)	166.7(153.4)	<0.001	141.4(151.7)	129.9(85.5)	143.5(115.6)	144.5(127.9)	0.2
Vegetables (g/d) *	129.9(81.4)	128.3(104.5)	124.6(73.7)	153.9(102.8)	0.01	122.2(75.7)	127.1(102.4)	136.4(80.9)	150.9(104.0)	0.004
Grains (g/d) *	472.1(150.9)	382.5(121.5)	376.7(155.8)	399.5(176.2)	0.01	477.4(183.9)	409.9(154.7)	372.9(127.7)	369.8(130.4)	<0.001
Fat and oil (g/d) *	32.0(26.0)	30.0(14.4)	27.5 (11.5)	34.4 (24.9)	0.1	33.4 (23.9)	31.1 (14.2)	29.8 (12.9)	31.0 (20.3)	0.7

BMI = body mass index, SES = socio-economic status, * mean (SD)

Table 4. Multivariate adjusted ORs (95% CIs) for gastric cancer across the quartiles of red and white meat consumption.

	Quartile	Number of cases	Number of controls	[a]Row model	[b]Adjusted model
Red Meat	Q1	65	161	1	1
	Q2	36	162	0.55 (0.34 – 0.87)	1.02 (0.53 – 1.96)
	Q3	29	163	0.44 (0.27 – 0.71)	0.83 (0.41 – 1.66)
	Q4	60	161	0.92 (0.61 – 1.39)	1.87 (1.01 – 3.47)
				$P_{trend} = 0.001$	$P_{trend} = 0.07$
White meat	Q1	84	162	1	1
	Q2	33	162	0.39 (0.24 – 0.63)	0.50 (0.27 – 0.93)
	Q3	32	161	0.38 (0.24 – 0.60)	0.41 (0.21 – 0.78)
	Q4	41	162	0.48 (0.31 – 0.75)	0.36 (0.19 – 0.68)
				$P_{trend} = {<}0.001$	$P_{trend} = 0.005$

[a]Row model= Crude OR; [b]Adjusted model= adjusted for age (30–50, 51–70, >71 years old), sex (qualitative), energy intake (kcal/day), ethnicity (qualitative), hot tea consumption (qualitative), tooth brushing (yes/no), cigarette smoking (yes/no), SES (high, average, low), literacy (literate/illiterate), opium consumption (yes/no), grains intake (quartiles), dairy consumption (quartiles), and vegetable (quartiles) and fruit (quartiles) intake.

As mentioned earlier, a number of possible mechanisms are proposed to explain how meat intake might induce cancer. Meat is often regarded as both a high-fat and energy-dense food, and it is believed that animal fats and high energy density foods can yield to obesity which, in turn, might pose cancer risk.[10] Cooking meat at high temperatures can also provoke destructive reactions between amino acids and creatine to produce carcinogenic HCAs.[37] PAHs are another carcinogenic substances formed during cooking meat over intense and usually direct heat (grilling or barbequing).[38] Carcinogenic NOCs might be partially produced due to high hem content of meat or as a result of nitrite and nitrate reactions within the body. Nitrite and nitrate might be either added to meat during curing processes or naturally presented within dietary sources.[10] Besides, processed meat usually contains high amounts of salt and it is experimentally shown that high salt may impair gastric mucosa which can heighten carcinogenesis.[9]

We also observed a statistically significant reverse association between white meat intake and the risk of gastric cancer. Regarding fish consumption, so far, there has been incompatibility among the results of former studies.[39] While some have reported a statistically significant protective role against gastric cancer,[28,40,41] some others either reached no statistical significance[24,25,42] or showed a positive association.[21] Hence, a meta-analysis reached the conclusion that the existing evidence still shows an unclear relation between fish consumption and gastric cancer.[39]

Fish contains high amounts of polyunsaturated fatty acids (PUFAs) which are suggested to hinder carcinogenesis.[41,43] It is also postulated that NOCs might be less probable to be produced endogenously during the consumption of white meat.[44] On the other hand; however, fish has the propensity to accumulate pollutants that may contain carcinogenic heavy metals or organic compounds which mainly store within its fat deposits.[45]

The evidence regarding poultry consumption and the risk of gastric cancer is so confined in quantity and consistency that conclusive results cannot be drawn.[9] On the one hand, some of these limited studies have reported an inverse association of no statistical significance,[25,31] and on the other hand, some others have shown a statistically significant[46] or non-significant[11,30] positive association in this regard.

Our study has some notable strength in comparison to similar case-control studies. The big plus is that it is a population-based study with a neighborhood control design. It is shown that these controls are superior to hospital-based ones in the study of upper gastrointestinal cancers in this region.[47] Histologic confirmation of cases and use of validated questionnaires to collect dietary

and lifestyle information should be mentioned as well. Another worth- mentioning point of this study is that *H. pylori* infection was determined using *H. pylori* multiplex serology which has a high-throughput for assessing *H. pylori* prevalence compared to similar methods.[18] Despite the fact that *H. pylori* infection is an established risk factor for gastric cancer,[48,49] we observed no statistically significant difference between the case and control groups regarding *H. pylori* infection. A rational explanation of this observation might be the high prevalence of *H. pylori* infection in the Iranian context.[5] Besides, the majority of *H. pylori*-infected individuals in Iran are of CagA positive strain.[5] Although there is no ambiguity in the association between CagA positive *H. pylori* and non-cardia gastric cancer,[50,51] the role of CagA positive *H. pylori* infection in the risk of cardia gastric cancer is still vague in some research.[52,53]

Some of the limitations of this study are those inherent to case-control designs, including recall bias, particularly with regard to FFQ data. Besides, some limitations are specific to the study itself. Although there was a serious attempt to gather information regarding all known risk factors that may influence the results of the study, we lacked data on physical activity and family history of gastric cancer which can potentially confound our estimates. Lack of information regarding different methods of cooking and meat preparation was also another limitation of the study. However, some studies have not reached the conclusion that cooking meat at high temperatures or heterocyclic amines might be related to gastric cancer. [32,54] Finally, we could not distinguish between histologic subtypes of gastric cancers due to lack of adequate data.

In summary, we found a positive association of total red meat consumption and gastric cancer risk, whereas white meat consumption was inversely associated with the risk.

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